REC'D 06 SEP 2005
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
4-33220A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/006794	23.06.2004	24.06.2003
International Patent Classification (IPC) or national classification and IPC		
C07K14/655, A61K38/31, C07K7/06		
Applicant		
NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.04.2005	05.09.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Döpfer, K-P Telephone No. +49 89 2399-8547

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006794

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

2-24	as originally filed
1	filed with the demand

Claims, Numbers

1-10	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006794

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9 (Industrial Applicability)

because:

☒ the said international application, or the said claims Nos. 9 (Industrial Applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006794

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I
Basis of the report

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 9 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: WO 02/10192 A (NOVARTIS ERFIND VERWALT GMBH ; ALBERT RAINER (CH); LEWIS IAN (CH); NOV) 7 February 2002 (2002-02-07)
   D2: WO 97/01579 A (SANDOZ AG ; ALBERT RAINER (CH); LEWIS IAN (CH); BAUER WILFRIED (CH); S) 16 January 1997 (1997-01-16)
   D3: US-A-4 612 366 (NUTT RUTH F) 16 September 1986 (1986-09-16)
   D4: REUBI J C ET AL: "A new peptidic somatostatin agonist with high affinity to all five somatostatin receptors" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 456, 2002, pages 45-49, XP002276363 ISSN: 0014-2999

2. *Novelty and Inventive Step (Article 33(2)(3) PCT)*

2.1 The present application addresses pharmaceutical compositions for parenteral administration with somatostatin analogues comprising the amino acid sequence -

(D/L)Trp-Lys-X_1-X_2- with the definitions of X_1 and X_2 as described in the application documents as filed and tartaric acid.

2.2 D1 discloses a compound (called compound A) differing only in the absolute configuration at the α-carbon atom of the phenylglycine preceding to the Trp. All diastereomers are contemplated and as well pharmaceutical compositions suitable for parenteral administration are described, but not with tartaric acid. Present claims 1-9 are thus considered novel in view of D1. The compound of present claim 10 is not explicitly disclosed although all diastereromeric species are contemplated in D1. This compound is therefore novel by selection.

D2 addresses somatostatin peptides and pharmaceutical compositions in general. The use of tartrate has not been mentioned. Claims 1-9 are therefore considered novel in view of D2.

D3 and D4 represent background art background art disclosing cyclic somatostatin analogues which are not encompassed by the general formula mentioned above. Parenteral administration is contemplated in D3 (see example 9). No particular pharmaceutical compositions are mentioned. D4 addresses peptidic somatostatin agonists with high affinity to all five somatostatin receptors. The peptides are structurally distinct. Their potential application was contemplated as anti-cancerous agents. D3 and D4 are not pertinent of the subject-matter of present claims 1 to 10.

D1 is regarded as representing the closest prior art. It discloses pharmaceutical compositions comprising compounds which differ in the absolute configuration of the α-C atom of the phenylglycine and in the use of aspartate as a further ingredient. These pharmaceutical compositions are applied parenterally to the recipients in order to treat *inter alia* acromegaly as well as tumours.

The distinguishing features tartrate (for claims 1 to 9) results in good tolerableness and high stability.
The particular stereoisomeric form appears to have no particular effect in view of the prior art.

The problem underlying the present application can be seen as to provide stable and highly tolerable formulations of compounds of the general formula I.
The closest prior art D1 as well as D2 contemplate the parenteral application of cyclic somatostatin analogues for the treatment of the same diseases with the exception of Cushing's disease (present claim 8). None of the documents mentions the problem of pain during i.v. or s.c. injection, neither is mentioned the lack of stability of pharmaceutical compositions comprising compounds of general formula I.

The solution of the technical problem posed is the addition of tartrate to the injection composition. This suggested solution essentially corresponds to the features which distinguish the invention from the prior art.

The skilled person faced with the problem to be solved gets no hints from the closest prior art alone or in combination with D2 in order to come to the proposed solution.

Present claims 1-9 are therefore considered involving an inventive step.

Claim 10 addresses a compound which is distinguished by the prior art documents only in the absolute configuration at C-atom 2. This new spatial arrangement results in a different affinity to several hsst sub-types.

D1 is regards as the closest prior art, too.
It discloses compound B which is compound A with the opposite configuration at C-atom 2.

The problem underlying the present application concerning the subject-matter of claim 10 is regarded as to provide further somatostatin analogue with a modified affinity pattern ti hsst sub-types.

D1 contemplates the change in the stereochemistry at C-atom 2 of compound A. The change in affinities to the hsst sub-types could be expected, although the exact affinity pattern was not derivable from the prior art. Nevertheless, the modification at C-atom 2 is considered within the normal experimentation of the skilled person and the result is not particularly surprising. The subject-matter of present claim 10 is

therefore regarded as lacking an inventive step.

2.3 *Industrial applicability (Article 33(4) PCT*

The subject-matter of present claims 1-8 and 10 appear to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

Re Item VIII

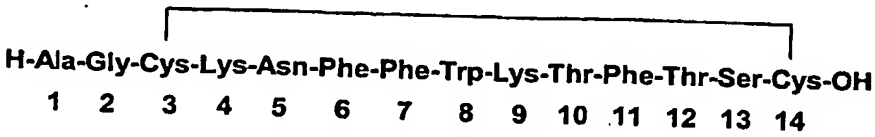
Certain observations on the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

Pharmaceutical Composition

The present invention relates to parenteral pharmaceutical compositions comprising a somatostatin analogue and to novel somatostatin analogues.

Somatostatin is a tetradecapeptide having the structure

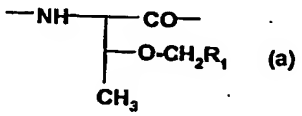


Since the isolation and characterization of somatostatin, an extensive search for more potent and more stable analogues has continued.

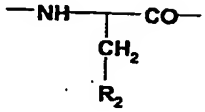
Somatostatin analogues have been described e.g. in WO 97/01579. Said somatostatin analogues comprise the amino acid sequence of formula I.

-(D/L)Trp-Lys-X_1 -X_2 - I

wherein X_1 is a radical of formula (a) or (b)



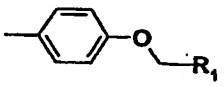
(a)

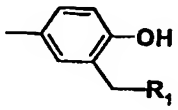


(b)

wherein R_1 is optionally substituted phenyl,

R_2 is $-Z_1-CH_2-R_1$, $-CH_2-CO-O-CH_2-R_1$,



or


wherein Z_1 is O or S, and

X_2 is an α-amino acid having an aromatic residue on the C_α side chain, or an amino acid unit selected from Dab, Dpr, Dpm, His,(Bzl)HyPro, thienyl-Ala, cyclohexyl-Ala and t-butyl-Ala, the residue Lys of said sequence corresponding to the residue Lys^9 of the native somatostatin-14.

By somatostatin analogue as used herein is meant a straight-chain or cyclic peptide derived from that of the naturally occurring somatostatin-14, comprising the sequence of formula I and wherein additionally one or more amino acid units have been omitted and/or replaced by